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ORIGINAL ARTICLE

Metabolic Syndrome in Inflammatory Bowel Disease: A Real Relationship or Just a Coincidence

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ABSTRACT

Background and aim: Presence of metabolic syndrome along with inflammatory diseases is being reported with increased frequency. The aim of this study was to investigate the presence of metabolic syndrome in inflammatory bowel disease patients.

Materials and methods: Fifty-one patients with ulcerative colitis, 34 patients with Crohn's disease and 88 healthy controls were included in this study. All of the patients were in remission state. Subjects were classified as having the metabolic syndrome based on the National Cholesterol Education Program (NCEP) and the modified World Health Organization (WHO) definition.

Results: The prevalence of metabolic syndrome in patients with ulcerative colitis was 16% according to the NCEP and 23.5% according to the WHO, and that in patients with Crohn's disease was 8.8% according to the NCEP and 14.7% according to the WHO. The prevalence of metabolic syndrome in control group was 18% according to the NCEP and 15.7% according to the WHO. When inflammatory bowel disease patients and control groups were compared with respect to the presence of metabolic syndrome, there was no statistically significant difference between the two groups according to neither NCEP nor WHO.

Conclusion: Although it is predicted that metabolic syndrome develops lesser since inflammatory bowel disease patients as they are considered to have lower body mass index, frequency of metabolic syndrome is not less than control group according to the results of our study. Therefore, possibility of metabolic syndrome in inflammatory bowel disease patients should not be overlooked and it should be considered that it can be used in patient follow-up.

Abbreviations: IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; TNF: Tumor necrosis factor; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; CDAI: Crohn disease activity Index; BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IR: Insulin resistance; EGIR: European group for the study of insulin Resistance; NCEP: National cholesterol education program; ACE: American college of cardiology; IDF: International diabetes federation.

Keywords: Metabolic syndrome, Ulcerative colitis, Crohn's disease, Insulin resistance.

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INTRODUCTION

The term inflammatory bowel disease (IBD) describes a group of chronic, recurrent intestinal disorders, each with a complex pathogenesis. The two most common are Crohn's disease (CD) and ulcerative colitis (UC). UC and CD are characterized by inflammation independent from any known etiologic factors, such as infection, medicines, ischemia and radiation with a cause and mechanism not precisely known.[1,2]

Various studies have shown that pathogenesis of metabolic syndrome involves an inflammatory process. Proinflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha) cause insulin resistance via blocking the activity of insulin.[3] Insulin resistance is closely associated with obesity. However, systemic inflammation, anorexia, malabsorption and weight loss as a result of chronic diarrhea are one of the most prominent characteristics of IBD. Presence of metabolic syndrome in patients with inflammatory diseases has been reported increasingly day by day. By virtue of this relation between metabolic syndrome and inflammation, the frequency of metabolic syndrome was studied in rheumatoid arthritis (RA)[4] and systemic lupus erythematosus (SLE),[5] and increased prevalence of metabolic syndrome in these diseases has been reported. It has also been reported that early atherosclerosis and increase in cardiac arterial thromboembolic events occur in IBD patients.[6] Although there are reports regarding the role of metabolic syndrome in some gastrointestinal diseases,[7] the correlation of metabolic syndrome with IBD is not known. Considering these information, the aim of this study was to investigate the presence of metabolic syndrome in IBD patients.

MATERIALS AND METHODS

Patients with quiescent CD or UC who were admitted to gastroenterology outpatient clinic and were between 18 and 65 years of age were enrolled in this cross-sectional study. Disease duration, clinical features, history, smoking habit, current and cumulative medication of the patients were determined from the information provided by patients and medical record. In CD patients, disease activity was measured with the use of the Crohn disease activity index (CDAI). When the CDAI score was <150, the disease considered inactive. In UC patients, disease activity was measured with Truelove-Witts and/or Mayo criteria. Patients with the following criteria were excluded from this study: (1) Patients receiving steroids during the study, (2) patients who had received steroids within last 6 months prior to study period, (3) patients receiving anti-TNF agents. Since drugs used in active period (e.g. steroids) can influence the diagnostic criteria of metabolic syndrome, patients in remission were included in the study.

All of the subjects were questioned about the presence of hypertension and cigarette smoking. Height, body weight and waist circumferences were measured and body mass index (BMI) was calculated (kilogram per square meter). Blood pressure was determined as the average of two measurements obtained 5 minutes apart after subjects had rested in supine position for at least 10 minutes Fasting blood samples were collected for the measurement of serum glucose, LDL cholesterol, HDL cholesterol, triglyceride, insulin and C-reactive protein (CRP) levels. Erythrocyte sedimentation rate (ESR) and complete blood count were also measured. Triglyceride levels were measured by Roche/Hitachi Modular D 2400 autoanalyzer with enzymatic method (Roche, Germany) and HDL cholesterol levels by Roche c16000 autoanalyzer enzymatically with polythelene glycol-modified enzymes. ESR was measured by the Westergren method having a normal range of <15 mm/1st hour. Insulin levels were measured by UniCel D×I 800 (Beckman Coulter, USA) autoanalyzer with Chemiluminescent enzyme immunoassay method (Beckman Coulter, USA). Insulin resistance (IR) was determined by using homeostasis model assessment of insulin resistance (HOMA-IR) index [fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5].[8]

Metabolic Syndrome Definitions

Subjects were classified as having the metabolic syndrome based on the national cholesterol education program (NCEP) and the modified World Health Organization (WHO) definition. NCEP guidelines classify individuals as having the metabolic syndrome, if they possess three or more of the following components:[9] (1) Fasting plasma glucose ≥110 mg/dl or receiving antidiabetic drugs; (2) hypertension (systolic and/or diastolic BP > 130/85 mm Hg or receiving antihypertensive drugs); (3) fasting plasma triglycerides >150 mg/dl; (4) fasting HDL cholesterol < 40 mg/dl or <50 mg/dl in males and females, respectively and (5) central obesity (waist circumference >102 cm or >88 cm in males and females respectively).

The WHO definition requires the presence of insulin resistance defined by any of following three criteria: A (HOMA-IR) index in the top quartile of a population without diabetes, impaired fasting glucose (≥110 mg/dl) or diabetes. In addition, two of the following three criteria are also required: (1) Central obesity (waist >94 cm in men and >88 cm in women), (2) dyslipidemia (triglycerides ≥150 mg/dl or HDL < 40 mg/dl in women or <35 mg/dl in men, (3) high blood pressure: ≥140/90 mm Hg or use of drugs for hypertension. On the basis of the study of inherited risk of coronary atherosclerosis data, we defined a HOMA-IR index > 2.114 as representing the top quartile of a population without diabetes.[10]

Written informed consent was obtained according to the declaration of Helsinki from all subjects before participation.

STATISTICAL ANALYSIS

Statistical analysis was performed by using a NCSS 2007 package program. During the evaluation of the study data, independent t-test was used regarding the comparisons of descriptive statistical methods (mean, standard deviation) as well as the comparisons of the groups and Chi-square test was used for comparison of qualitative data. Results were assessed at significance level of $p < 0.05$.

RESULTS

Fifty-one patients with UC (33 male), 34 patients with CD (24 female and 10 male) and 88 healthy controls (40 male) were included in this study. All of the patients with IBD were in remission state.

Of the patients with UC, 39.21% had pancolitis, 33.33% had left-sided UC, and 27.45% had distal UC and 84.31% were receiving 5-aminosalicylates and 15.68% were receiving immunosuppressive agents. Of the patients with CD, 29.41% were receiving 5-aminosalicylates and 70.58% were receiving immunosuppressive drugs. Of the patients with IBD, 44.7% were between 20 and 40 years of age, 44.7% were between 40 and 60 years of age and 10.6% were >60 years of age. Mean age of the patients with IBD was 42.9 ± 13.7 years, whereas it was 39.2 ± 11.9 years in control group. There was no statistical difference between the two groups with respect to age and gender ($p = 0.056$ and $p > 0.05$ respectively).

Mean BMI of the patients with IBD was 26.5 ± 5.1, whereas it was 27.3 ± 5.6 in control group ($p = 0.333$). While insulin resistance was present in 69.56% of the patients in IBD group, it was present in 35.38% of the patients in control group ($p = 0.003$).

The prevalence of metabolic syndrome in patients with UC was 16% according to the NCEP and 23.5% according to the WHO, and that in patients with CD was 8.8% according to the NCEP and 14.7% according to the WHO criteria. The prevalence of metabolic syndrome in control group was 18% according to the NCEP and 15.7% according to the WHO. When IBD and control groups were compared with respect to the presence of metabolic syndrome, there was no statistically significant difference between the two groups according to neither NCEP nor WHO ($p = 0.458$, $p = 0.364$) (Table 1). There was no statistically significant difference between UC and control groups with respect to the presence of metabolic syndrome according to neither NCEP nor WHO ($p = 0.414$, $p = 0.195$). There was no statistically significant difference between CD and control

Table 1: BMI and prevalence of insulin resistance and metabolic syndrome in patients with IBD and control group

		IBD group		Control group	p-value
		UC	CD		
BMI			26.55 ± 5.05	27.23 ± 5,64	0.333
IR			69.56%	35.38%	0.003
MS	NCEP	16%	8.8%	18%	0.458
	WHO	23.75%	14.7%	15.70%	0.364

UC: Ulcerative colitis; CD: Crohn's disease; IR: Insulin resistance; MS: Metabolic syndrome

groups with respect to the presence of metabolic syndrome according to neither NCEP nor WHO (p = 0.393, p = 0.993).

There was no statistically significant difference between UC and control groups with respect to the presence of metabolic syndrome according to neither NCEP nor WHO (p = 0.319, p = 0.513).

There were no statistically significant differences between patients with and without metabolic syndrome in IBD group with respect to gender, disease duration, smoking and drug used according to NCEP (p = 0.579, p = 0.592, p = 0.321 and p = 0.081 respectively)

There were no statistically significant differences between patients with and without metabolic syndrome in IBD group with respect to gender, disease duration, smoking and drug used according to NCEP (p = 0.65, p = 0.510, p = 0.483 and p = 0.240 respectively).

There was significant correlation between advanced age and the presence of metabolic syndrome in patients with IBD according to both NCEP and WHO (p = 0.025 and 0.025 respectively). There was significant correlation between high BMI and the presence of metabolic syndrome in patients with IBD according to both NCEP and WHO (p = 0.007 and p = 0.000, respectively). In patients with UC, there was no statistically significant difference between those with pancolitis, left-sided UC and distal UC with respect to the presence of metabolic syndrome according to neither NCEP nor WHO (p = 0.351, p = 0.261).

DISCUSSION

Metabolic syndrome is composed of some metabolic abnormalities including obesity. It is suggested to be a risk factor for cardiovascular and some other chronic diseases. The relationship between obesity, one of the most important components of metabolic syndrome and gastrointestinal system diseases has been described. It is well known that development of colorectal cancer, gastroesophageal reflux disease and obesity are closely related with obesity.[11] Obesity is a subject that should be emphasized for predisposition to the development of malignancy in patients with long-term IBD.[12] There are also reports regarding obesity can be related to IBD activity.[13] There is evidence regarding hypertrophied mesenteric adipose tissue increases the disease activity and leads to development of complications in CD.[14] Despite this preliminary information, relationship between metabolic syndrome and IBD is not clear.

The term metabolic syndrome is used to identify patients who are at increased risk of cardiovascular disease and diabetes.[15] WHO was the first to propose criteria for the diagnosis of metabolic syndrome[16] followed by the European Group for the study of Insulin Resistance (EGIR)[17] and the NCEP Adult Treatment Panel III,[18] American College of Cardiology (ACE)[19] and International Diabetes Federation (IDF).[20] Although these definitions proposed to identify patients at high-risk, they suggest different combinations and different cutoff points. NCEP definition do not require the measurement of insulin levels in its criteria, whereas WHO definition do require the assessment of insulin sensitivity or insulin levels. In WHO definition the presence of insulin resistance is the cornerstone. By restricting high-risk patients to individuals with high insulin levels rather than the general population, WHO criteria identifies only insulin resistant individuals with metabolic syndrome and misses many individuals who are at increased risk of cardiovascular diseases but without elevated insulin levels.[21] In a study from Turkey, it was shown that NCEP criteria categorize twice more subjects as metabolic syndrome than WHO criteria (38% *vs* 19% respectively). Similar results were reported from other studies. San Antonio Heart Study showed that NCEP had higher sensitivity than did the WHO definition. Hoorn study reported that NCEP definition was associated with an approximately 2-fold increased risk in all end points compared to WHO definitions.[22,23] Since there is not consensus on diagnostic criteria for metabolic syndrome, we performed our assessments on both of two criteria in our study.

There is very few information in the literature about association between IBD and metabolic syndrome. In our study, while the prevalence of metabolic syndrome was 16% NCEP and 23.5% WHO in UC group, it was 8.8% NCEP

and 14.7% WHO in CD group. We did not find a difference between control group and the groups with UC and CD with respect to the presence of metabolic syndrome. In one study, the prevalence of metabolic syndrome was 23% in UC and 7.1% in CD (p = 0.089) according to NCEP and was similar to general population. Since authors encountered higher metabolic syndrome prevalence especially in IBD patients with older age, they reported that those patients should be investigated for metabolic syndrome.[24] Our results were consistent with these studies. While mean ages of the patients with and without metabolic syndrome in IBD group (WHO) were 49.52 ± 12.75 years 41.27 ± 13.51 years, respectively (p = 0.025). The difference between them was also statistically significant according to NCEP.

It is suggested that metabolic syndrome is directly related to inflammation. Since it was expected to encounter higher prevalence of metabolic syndrome in pancolitis patients with extensive disease involvement considered to be present much more inflammation due to this reason, we could not find any finding supporting this in our study.

It is well known that cardiovascular disease risk increases in IBD patients. Systemic inflammation is one of the major reasons. Increased insulin resistance (IR) is an important risk for CVD. Increased insulin resistance is reported in IBD.[25] The rate of insulin resistance in patient group of our study is also 69.56%. Increased IR is also encountered in patients with autoimmune diseases.[26,27] Several important factors play a role in the pathogenesis of IR. TNF alpha is a proinflammatory cytokine and plays a major role in the pathogenesis of autoimmune diseases and inflammatory diseases. Many recently performed studies showed that TNF alpha might play an important role in insulin resistance in animal models. It was demonstrated that there was TNF alpha over expression in adipose tissue and skeleton system in patients with insulin resistance. It was seen that a decrease occurred in TNF alpha expression and secretion, and a reduction in TNF alpha levels and changes in insulin sensitivity of obese insulin resistant individuals. Interestingly, an increase in IR was determined when TNF alpha was applied to healthy volunteers.[28,29] The role of TNF alpha in the pathogenesis of IBD is well established and currently anti-TNF treatments gain gradually more importance.[30] TNF alpha might affect the course of disease also by facilitating the development of metabolic syndrome.

Although it is predicted that metabolic syndrome develops lesser since IBD patients are considered to have lower BMI, frequency of metabolic syndrome is not less than control group according to the results of our study. Also mean BMI of our study group is not low and it is within normal ranges and the rate of metabolic syndrome is at a comparable level to healthy controls. Limitation of our study is small number of cases and not inclusion of active patients with much more inflammation. If we consider that this study is a preliminary study, it is likely to attain relevant extensive data in future studies which will be performed with broad number of cases with active disease.

Neither etiological reasons of IBD nor pathogenesis of the complications caused by it are clear. Increased cardiac thromboembolic events and atherosclerotic process are important causes of mortality and morbidity for these patients. The importance of metabolic syndrome in these patients is known. Metabolic syndrome may be one of the many factors playing a role in the pathophysiology of IBD due to metabolic changes it caused. Therefore, possibility of metabolic syndrome in IBD patients should not be overlooked and it should be considered that it can be used in patient follow-up.

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